# Are non-surgical treatments for anal fissure effective?

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**Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure.** ***N Engl J Med*** **1999;341(2):65-9.**

## Research question

How do two non-surgical treatments (botulinum toxin [BT] and topical nitroglycerin [NTG] ointment) compare for treatment of chronic anal fissure?

## Type of article and design

Prospective, single-blind randomized trial.

## Relevance to family physicians

Anal fissure is a common problem that causes substantial discomfort in otherwise healthy people. Patients with anal fissure complain of rectal bleeding and pain during and after defecation. On examination, you might see a split in the skin of the distal anal canal; most anal fissures occur in the posterior midline. Multiple fissures or lateral fissures could be associated with other diagnoses, such as inflammatory bowel disease, tuberculosis, human immunodeficiency virus infection, or syphilis.

In the acute condition, anal fissures usually resolve with increased dietary fibre and sitz baths.[1] When fissures persist for longer than 6 to 8 weeks, other modes of treatment are usually indicated. Chronic anal fissures are believed to be associated with spasm and hypertonicity of the anal sphincter. While the exact causes of fissure persistence are not clear, some have suggested that sphincter spasms lead to relative ischemia of the anal canal, which complicates fissure healing. The most common treatments for chronic anal fissures are aimed at alleviating sphincter hypertonicity. This has been achieved surgically by lateral internal sphincterotomy, which is effective but can cause feces and flatus incontinence that is sometimes permanent.

Pharmacologic methods can be used to create the effect of reversible sphincterotomy, reducing sphincter pressure until the fissure has healed. These methods may be used by family physicians when fissures fail to heal with more conservative measures. Botulinum toxin and NTG ointment have each been shown superior to placebo.[2,3] This study compares these two treatments.

## Overview of study and outcome

Fifty adults with symptomatic chronic posterior anal fissures were randomized to receive treatment with 20 U of BT injected into the internal anal sphincter on each side of the anterior midline or 0.2% NTG ointment applied twice daily for 6 weeks. Diagnosis required evidence of a posterior circumscribed ulcer, with a sentinel tag of skin, induration at the edges, and exposure of the horizontal fibres of the internal anal sphincter; and symptoms (postdefecation or nocturnal pain, bleeding, or both) lasting more than 2 months. Patients with acute fissures or fissures associated with other conditions (eg, inflammatory bowel diseases, HIV, hemorrhoids, fistula-in-ano, anal abscesses, or cancer) and those who had had previous anal surgery were excluded.

Baseline assessment included clinical inspection of the fissure and anorectal manometry at rest and after maximal voluntary contraction. These evaluations were repeated 1 and 2 months after treatment.

Treatment for the BT group consisted of injections of BT-A diluted in saline to a concentration of 50 U/mL. The internal sphincter was palpated and injected with a 27-gauge needle while patients were in the left lateral position. Each patient received two injections of 0.2 mL of solution (10 U) on each side of the anterior midline of the internal anal sphincter. No sedation or local anesthesia was used during the procedure.

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Treatment for the NTG group consisted of 0.2% NTG ointment prepared from 2 g of 2% NTG diluted to 100 g with soft paraffin. About 1.2 g of ointment (determined with a dose regulator) were applied by patients to their anuses and anal canals twice daily for 6 weeks.

At each visit, patients were offered the opportunity to drop out of the study and undergo lateral internal sphincterotomy. After 2 months, patients with persistent fissures were offered the alternative pharmacologic treatment; these patients were then evaluated according to the same protocol. Patients with healed fissures were followed clinically for at least 11 months.

Primary outcomes were resolution of symptoms, resolution of fissure, and anal manometry results.

## Results

The study enrolled 50 consecutive outpatients with chronic posterior anal fissures. Groups were similar at baseline with regard to age, sex, duration of symptoms, and resting and maximal voluntary pressures. All patients reported severe pain after defecating and all had clinically apparent posterior anal fissures with sentinel tags of skin and exposed fibres of the internal anal sphincter.

One month after treatment, fissures had healed in 22 patients in the BT group (88%) and in 10 in the NTG group (40%) ($P$ <.001). Another two patients in the BT group and 10 in the NTG group had reduced symptoms. One patient in the BT group and seven in the NTG group had persistent symptomatic fissures. At the 2-month evaluation, fissures had healed in 24 patients in the BT group and in 15 in the NTG group.

No complications of injection or adverse events were reported in the BT group. Five patients in the NTG group reported moderate-to-severe headaches after ointment application at some time during the course of treatment. The headaches were transient (30 to 40 minutes) and were relieved by oral analgesia. One of these patients withdrew from the study because of headaches. Two patients reported moderate burning in the anal area. There were no reports of fecal incontinence.

Resting anal pressures were significantly reduced from baseline in both groups, but were lower among patients in the BT group at 2 months. Maximal voluntary pressure did not differ significantly from baseline in either group.

Patients in the BT group were followed for an average of 15.4 months, during which there were no relapses, complications, or side effects. One patient in the BT group whose fissure persisted was treated with NTG and had healed completely 2 months later. Average follow up for the NTG group was 16.1 months, during which there were no relapses, complications, or side effects. The one patient in the NTG group who withdrew underwent lateral sphincterotomy. Nine patients with persistent fissures in the NTG group were treated with BT and their fissures had completely healed within 2 months.

## Analysis of methodology

This study expands on previous placebo-controlled trials of BT and NTG ointment. In this context, it was well designed. Assignment of patients to treatment groups was randomized by computer. Follow up was excellent. Only one patient failed to complete the treatment, and all enrolled patients were followed for a minimum of 11 months past the treatment date. The clinical examiners were blind to patients' treatment assignments, but unfortunately, patients were not blinded to their treatment, and it is not clear whether they were instructed not to reveal their treatment groups to the examiners.

The groups were relatively similar at the start of the trial. Mean duration of symptoms was higher in the NTG group than in the BT group, but the standard deviations of the means were wide (BT group, 9.5 months [± 6.8]; NTG group, 14.7 months [± 10.7]). Apart from study medications, groups were treated equally. The effects of treatment were large and statistically significant, and the authors considered most important clinical outcomes.

The authors did not describe the study setting. Participants were outpatients probably recruited in a surgical or speciality clinic. Patients in tertiary settings likely have more serious fissures than patients who present to family doctors' offices.

## Application to clinical practice

In this trial, injection of BT was found more effective for chronic anal fissures and had fewer side effects than treatment with NTG ointment. After 2 months, fissures had healed in 96% of patients treated with BT and in 60% of those treated with NTG. Previous studies have shown both treatments to be more effective than placebo.

Lund and Scholefield[3] compared NTG ointment with placebo for chronic fissures. In that study, 68% of patients receiving NTG healed compared with 8% of patients receiving placebo (n = 80).[3,4] Studies that compared BT injections with placebo demonstrated healing rates from 60% to 76% for BT.[2,5] The surgical alternative, lateral internal sphincterotomy, results in healing for 90% to 95% of patients, but it can cause irreversible incontinence.

Compared with treatment with NTG ointment, treatment with BT showed an absolute risk reduction of

36%. Number needed to treat with BT to heal one fissure (that would not have healed with NTG) was 2.8. From the study by Lund and Scholefield,[3] we can estimate that the number needed to treat with NTG to heal one fissure (that would not have healed with placebo) is 1.7. For every five people treated with NTG ointment, one will have moderate-to-severe headaches, and for every 12.5 people, one will have anal burning.

Botulinum toxin is expensive. A 100-U vial costs pharmacists $325. Treatment requires a physician who can competently inject the internal anal sphincter. Studies where BT was injected into the external sphincter, however, also demonstrated a treatment effect.[5] Nitroglycerin ointment is inexpensive and requires less skill to apply: a large tube of 2% ointment costs less than $15.

For acute fissures, one study demonstrated an 87% healing rate in first episodes of acute fissure using sitz baths and dietary unprocessed bran. This was a significantly better rate of healing than with hydrocortisone or lidocaine ointment. A well designed study published in August 1999[6] found significantly better healing with 0.2% nifedipine gel applied twice daily for 3 weeks than with hydrocortisone and lidocaine cream (95% versus 50%). In this study, both groups also changed their diets and used laxatives and anal dilators.

## Bottom line

- Botulinum toxin injection is a safe and effective treatment for chronic anal fissures. Botulinum toxin injections are more effective and less likely to cause adverse effects than treatment with NTG ointment. Injection of BT might have comparable efficacy to lateral internal sphincterotomy and is less likely to cause irreversible incontinence of flatus or stool.
- Nitroglycerin is a relatively effective treatment for chronic fissures and might be useful as a first-line pharmacologic treatment for physicians who are not comfortable injecting the internal sphincter with BT. Patients should be advised of the risk of transient headaches and anal burning.
- For acute fissures, physicians can recommend warm sitz baths and unprocessed bran. It would be reasonable to prescribe NTG ointment for acute fissures, although there is limited evidence for its effectiveness in this context. Physicians might also consider nifedipine gel for acute fissures in light of recent promising evidence.

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